REMARKS

Claims 2-15, 19-24, 26-32, 34-39, 41-49 and 51-52 are canceled. Claims 1, 16, 17, 18, 25 and 33 were entered by the PTO, as amended in Applicants Preliminary Amendment of March 15, 2001. Claims 40 and 50 are present as originally filed. With this Amendment, Claims 1, 16, 17, 18, 25 and 33 have been amended. New Claims 53-75 have been added. After entry of the amendment, Claims 1, 16-18, 25, 33, 40, 50 and 53-75 are pending. A version of the Claims with markings to show changes made is attached at Exhibit A. For the Examiner's convenience, a clean copy of the pending claims after entry of the instant amendment is attached at Exhibit B.

I. THE AMENDMENT OF THE CLAIMS

In general, the claims have been amended to recite D-enantiomeric ApoA-I agonist peptides and multimers of ApoA-I agonist peptides. The amendments are fully supported by the specification, for example, at page 42, lines 11 to 34 and page 44, line 15 to page 45, line 4. New Claims 53-75 recite additional ApoA-I agonist compounds, lipid complexes, pharmaceutical compositions and methods of use thereof. Support for new Claims 53-75 can be found in the specification, for example, at page 48, line 17 to page 49, line 19; page 75, line 8 to page 76, line 15; page 76, line 19 to page 80, line 18; page 80 line 29 to page 84, line 23.

As the amendments and new claims are fully supported by the specification, entry thereof is respectfully requested. Applicants thank the Examiner for his cooperation in readying the claims for examination.

CONCLUSION

Applicants submit that Claims 1, 16-18, 25, 33, 40, 50 and 53-75 satisfy all the criteria for patentability and are in condition for allowance. An early indication of the same is therefore kindly solicited.

Pursuant to 37 C.F.R. §1.136 (a)(3), the Commissioner is authorized to charge all required fees, fees under 37 C.F.R. §1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds LLP, U.S. Deposit Account No. 16-1150 (Order No. 9196-019-999). A Fee Transmittal Sheet is enclosed (in duplicate) for accounting purposes.

Respectfully submitted,

Date: October 16, 2002

42,983
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EXHIBIT A

Claim Amendment: Marked Up Copy

1. (Twice amended) An ApoA-I agonist compound comprising:

(i) an 18 to 22-residue D-enantiomeric peptide or peptide analogue which forms an amphipathic α-helix in the presence of lipids and which comprises formula (I):

Z_1-X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14}-X_{15}-X_{16}-X_{17}-X_{18}-Z_2

X_1 is D-Ala (a), Gly (G), D-Asn (n), D-Gln (q) or D-Pro (p);

X_2 is a D-enantiomeric aliphatic residue;

X_3 is D-Leu (l);

X_4 is a D-enantiomeric acidic residue;

X_5 is D-Leu (l) or D-Phe (f);

X_6 is D-Leu (l) or D-Phe (f);

X_7 is a D-enantiomeric basic residue;

X_8 is a D-enantiomeric acidic residue;

X_9 is D-Leu (l) or D-Trp (w);

X_{10} is D-Leu (l) or D-Trp (w);

X_{11} is a D-enantiomeric acidic residue or D-Asn (n);

X_{12} is a D-enantiomeric acidic residue;

X_{13} is D-Leu (l), D-Trp (w) or D-Phe (f);

X_{14} is a D-enantiomeric basic residue or D-Leu (l);

X_{15} is D-Gln (q) or D-Asn (n);

X_{16} is a D-enantiomeric basic residue;

X_{17} is D-Leu (l);

X_{18} is a D-enantiomeric basic residue;

Z_1 is RRN-, or RC(O)NR-;

Z_2 is -C(O)NRR, -C(O)OR or -C(O)OH or a salt thereof;

each R is independently -H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, (C_5-C_{20}) aryl, (C_6-C_{26}) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl or a 1 to 7-residue peptide or peptide analogue in which one or more bonds between residues 1 through 7 are independently a substituted amide, an isostere of an amide or an amide mimetic;

each " - " between residues X_1 through X_{18} independently designates an amide linkage, a substituted amide linkage, an isostere of an amide or an amide mimetic; or

(ii) a 14 to 21- residue deleted D-enantiomeric peptide or peptide analogue according to formula (I) in which at least one and up to eight of residues X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9, X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17} and X_{18} are optionally deleted; or

(iii) an [18-22-] 18 to 22- residue altered D-enantiomeric peptide or peptide analogue according to formula (I) in which at least one of residues X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , X_7 , X_8 , X_9 , X_{10} , X_{11} , X_{12} , X_{13} , X_{14} , X_{15} , X_{16} , X_{17} and X_{18} is conservatively substituted with another D-enantiomeric residue.

16. (Twice amended) A multimeric ApoA-I agonist compound which comprises formula (II):

(II) $HH[LL_m\text{-}HH]_nLL_m\text{-}HH$

or a pharmaceutically acceptable salt thereof, wherein:

each m is independently an integer from 0 to 1;

n is an integer from 0 to 10;

each "HH" is independently a D-enantiomeric peptide or peptide analogue according to Claim 1;

each "LL" is independently a bifunctional linker; and

each " - " independently designates a covalent linkage.

17. (Twice amended) A multimeric ApoA-I agonist compound which comprises formula (III):

(III) $X\text{-}N_{ya}\text{-}X_{(ya-1)}\text{-}(\text{-}N_{yb}\text{-}X_{(yb-1)})_p$

or a pharmaceutically acceptable salt thereof, wherein:

each X is independently $HH\text{-}(\text{-}LL_m\text{—}HH\text{-})_nLL_m\text{—}HH$;

each HH is independently a D-enantiomeric peptide or peptide analogue according to Claim 1;

each LL is independently a bifunctional linker;

each m is independently an integer from 0 to 1;

each n is independently an integer from 0 to 8;

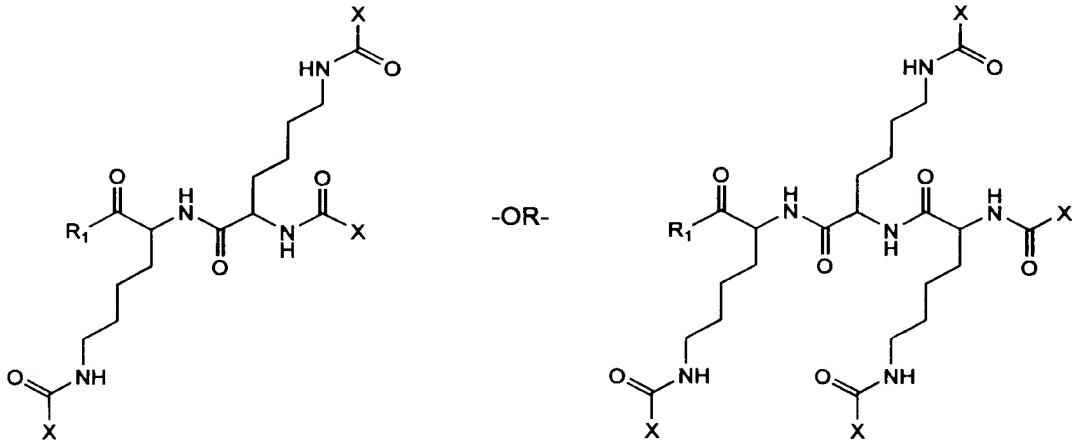
N_{ya} and N_{yb} are each independently a multifunctional linking moiety where y_a and y_b represent the number of functional groups on N_{ya} and N_{yb}, respectively;

each y_a or y_b is independently an integer from 3 to 8;

p is an integer from 0 to 7; and

each "—" independently designates a covalent bond.

18. (Twice amended) A multimeric ApoA-I agonist compound which comprises formula (IV) or (V):



(IV) (V)

or a pharmaceutically acceptable salt thereof, wherein:

each X is independently HH-(-LL_m—HH-)-$_n$$LL_m$—HH;

each HH is independently a D-enantiomeric peptide or peptide analogue according to Claim 1;

each LL is independently a bifunctional linker;

each n is independently an integer from 0 to 1;

each m is independently an integer from 0 to 8;

R_1 is -OR or -NRR; and

each R is independently -H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl[;], (C_5-C_{20}) aryl, (C_6-C_{26}) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl.

25. (Twice amended) An ApoA-I agonist-lipid complex comprising an ApoA-I agonist and a lipid, wherein the ApoA-I agonist is a D-enantiomeric peptide or peptide analogue according to Claim 1, a multimeric ApoA-I agonist compound according to Claim 16, a multimeric ApoA-I agonist compound according to Claim 17, or a multimeric ApoA-I agonist compound according to Claim 18.

33. (Twice amended) A pharmaceutical composition comprising an ApoA-I agonist and a pharmaceutically acceptable carrier, excipient or diluent, wherein the ApoA-I agonist is [in form of an ApoA-I agonist-lipid complex, said complex comprising an ApoA-I agonist compound and a lipid] a D-enantiomeric peptide or peptide analogue according to Claim 1, a multimeric ApoA-I agonist compound according to Claim 16, a multimeric ApoA-I agonist compound according to Claim 17, or a multimeric ApoA-I agonist compound according to Claim 18.

EXHIBIT B

Claim Amendment: Pending Claims After Entry of Instant Amendment

1. (Twice amended) An ApoA-I agonist compound comprising:

(i) an 18 to 22-residue D-enantiomeric peptide or peptide analogue which forms an amphipathic α-helix in the presence of lipids and which comprises formula (I):

Z_1-X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14}-X_{15}-X_{16}-X_{17}-X_{18}-Z_2

X_1 is D-Ala (a), Gly (G), D-Asn (n), D-Gln (q) or D-Pro (p);

X_2 is a D-enantiomeric aliphatic residue;

X_3 is D-Leu (l);

X_4 is a D-enantiomeric acidic residue;

X_5 is D-Leu (l) or D-Phe (f);

X_6 is D-Leu (l) or D-Phe (f);

X_7 is a D-enantiomeric basic residue;

X_8 is a D-enantiomeric acidic residue;

X_9 is D-Leu (l) or D-Trp (w);

X_{10} is D-Leu (l) or D-Trp (w);

X_{11} is a D-enantiomeric acidic residue or D-Asn (n);

X_{12} is a D-enantiomeric acidic residue;

X_{13} is D-Leu (l), D-Trp (w) or D-Phe (f);

X_{14} is a D-enantiomeric basic residue or D-Leu (l);

X_{15} is D-Gln (q) or D-Asn (n);

X_{16} is a D-enantiomeric basic residue;

X_{17} is D-Leu (l);

X_{18} is a D-enantiomeric basic residue;

Z_1 is RRN-, or RC(O)NR-;

Z_2 is -C(O)NRR, -C(O)OR or -C(O)OH or a salt thereof;

each R is independently -H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, (C_5-C_{20}) aryl, (C_6-C_{26}) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl or a 1 to 7-residue peptide or peptide analogue in which one or more bonds between residues 1 through 7 are independently a substituted amide, an isostere of an amide or an amide mimetic;

each " - " between residues X_1 through X_{18} independently designates an amide linkage, a substituted amide linkage, an isostere of an amide or an amide mimetic; or

(ii) a 14 to 21- residue deleted D-enantiomeric peptide or peptide analogue according to formula (I) in which at least one and up to eight of residues X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9, X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17} and X_{18} are optionally deleted; or

(iii) an 18 to 22- residue altered D-enantiomeric peptide or peptide analogue according to formula (I) in which at least one of residues X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , X_7 , X_8 , X_9 , X_{10} , X_{11} , X_{12} , X_{13} , X_{14} , X_{15} , X_{16} , X_{17} and X_{18} is conservatively substituted with another D-enantiomeric residue.

16. (Twice amended) A multimeric ApoA-I agonist compound which comprises formula (II):

(II) $HH\{LL_m\text{-}HH\}_nLL_m\text{-}HH$

or a pharmaceutically acceptable salt thereof, wherein:

each m is independently an integer from 0 to 1;

n is an integer from 0 to 10;

each "HH" is independently a D-enantiomeric peptide or peptide analogue according to Claim 1;

each "LL" is independently a bifunctional linker; and

each " - " independently designates a covalent linkage.

17. (Twice amended) A multimeric ApoA-I agonist compound which comprises formula (III):

(III) $X\text{-}N_{ya}\text{-}X_{(ya-1)}\text{-}(\text{-}N_{yb}\text{-}X_{(yb-1)})_p$

or a pharmaceutically acceptable salt thereof, wherein:

each X is independently $HH\text{-}(\text{-}LL_m\text{—}HH\text{-})_nLL_m\text{—}HH$;

each HH is independently a D-enantiomeric peptide or peptide analogue according to Claim 1;

each LL is independently a bifunctional linker;

each m is independently an integer from 0 to 1;

each n is independently an integer from 0 to 8;

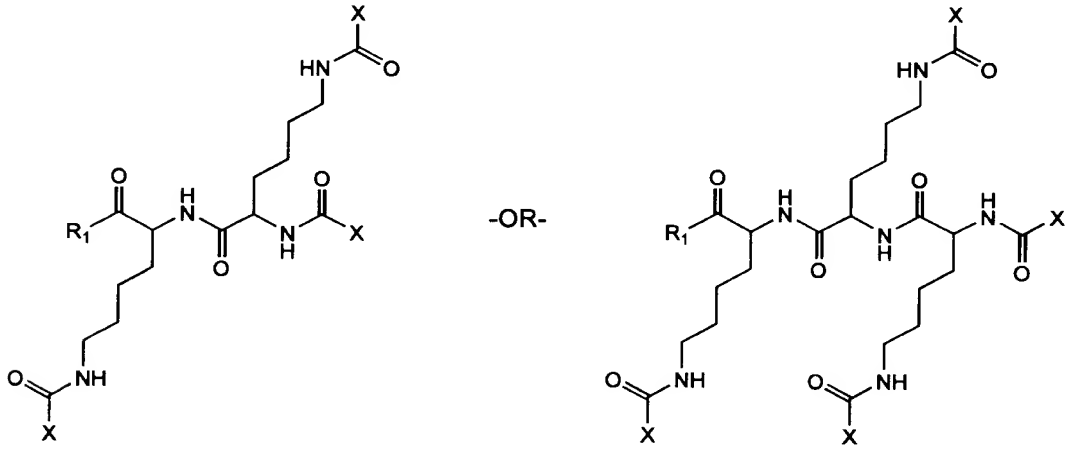
N_{ya} and N_{yb} are each independently a multifunctional linking moiety where y_a and y_b represent the number of functional groups on N_{ya} and N_{yb}, respectively;

each y_a or y_b is independently an integer from 3 to 8;

p is an integer from 0 to 7; and

each "—" independently designates a covalent bond.

18. (Twice amended) A multimeric ApoA-I agonist compound which comprises formula (IV) or (V):



(IV) (V)

or a pharmaceutically acceptable salt thereof, wherein:

each X is independently HH-(-LL_m—HH-)-$_n LL_m$—HH;

each HH is independently a D-enantiomeric peptide or peptide analogue according to Claim 1;

each LL is independently a bifunctional linker;

each n is independently an integer from 0 to 1;

each m is independently an integer from 0 to 8;

R_1 is -OR or -NRR; and

each R is independently -H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, (C_5-C_{20}) aryl, (C_6-C_{26}) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl.

25. (Twice amended) An ApoA-I agonist-lipid complex comprising an ApoA-I agonist and a lipid, wherein the ApoA-I agonist is a D-enantiomeric peptide or peptide analogue according to Claim 1, a multimeric ApoA-I agonist compound according to Claim 16, a multimeric ApoA-I agonist compound according to Claim 17, or a multimeric ApoA-I agonist compound according to Claim 18.

33. (Twice amended) A pharmaceutical composition comprising an ApoA-I agonist and a pharmaceutically acceptable carrier, excipient or diluent, wherein the ApoA-I agonist is a D-enantiomeric peptide or peptide analogue according to Claim 1, a multimeric ApoA-I agonist compound according to Claim 16, a multimeric ApoA-I agonist compound according to Claim 17, or a multimeric ApoA-I agonist compound according to Claim 18.

40. A method of treating a subject suffering from a disorder associated with dyslipidemia, said method comprising the step of administering to the subject an effective amount of the ApoA-I agonist compound of Claim 1.

50. A method of treating a subject suffering from septic shock, said method comprising the step of administering to the subject an effective amount of the ApoA-I agonist of Claim 1.

53. (New) The ApoA-I agonist compound of Claim 1 which is the altered D-enantiomeric peptide or peptide analogue according to formula (I).

54. (New) The ApoA-I agonist compound of Claim 53 in which the D-enantiomeric hydrophobic residues are fixed according to formula (I) and at least one non-fixed residue is conservatively substituted with another D-enantiomeric residue.

55. (New) The ApoA-I agonist compound of Claim 54 in which:

X_1 is D-Pro (p), Gly (G), D-Asn (n) or D-Ala (a);

X_2 is D-Ala (a), D-Leu (l) or D-Val (v);

X_3 is D-Leu (l);

X_5 is D-Leu (l) or D-Phe (f);

X_6 is D-Leu (l) or D-Phe (f);

X_9 is D-Leu (l) or D-Trp (w);

X_{10} is D-Leu (l) or D-Trp (w);

X_{13} is D-Leu (l), D-Trp (w) or D-Phe (f);X_{17} is D-Leu (l); and

at least one of X_4, X_7, X_8, X_{11}, X_{12}, X_{14}, X_{15}, X_{16} and X_{18} is conservatively substituted with another D-enantiomeric residue.

56. (New) The ApoA-I agonist compound of Claim 53 in which the D-enantiomeric hydrophilic residues are fixed according to formula (I) and at least one non-fixed residue is conservatively substituted with another D-enantiomeric residue.

57. (New) The ApoA-I agonist compound of Claim 56 in which:

X_4 is D-Asp (d) or D-Glu (e);

X_7 is D-Arg (r), D-Lys (k) or D-Orn;

X_8 is D-Asp (d) or D-Glu (e);

X_{11} is D-Asn (n) or D-Glu (e);

X_{12} is D-Glu (e);

X_{14} is D-Lys (k), D-Arg (r) or D-Orn;

X_{15} is D-Gln (q) or D-Asn (n);

X_{16} is D-Lys (k), D-Arg (r) or D-Orn;

X_{18} is D-Asn (n) or D-Gln (q); and

at least one of X_1, X_2, X_3, X_5, X_6, X_9, X_{10}, X_{13} and X_{17} is conservatively substituted with another D-enantiomeric residue.

58. (New) The ApoA-I agonist compound of Claim 56 in which X_3 is D-Leu (l), X_6 is D-Phe (f), X_9 is D-Leu (l) or D-Trp (w), X_{10} is D-Leu (l) or D-Trp (w) and at least one of X_1, X_2, X_5, X_{13} and X_{17} is conservatively substituted with another D-enantiomeric residue.

59. (New) The ApoA-I agonist compound of Claim 55 or 57 in which the substituting D-enantiomeric residue is classified within the same sub-category as the substituted D-enantiomeric residue.

60. (New) The ApoA-I agonist compound of Claim 1 which is the deleted D-enantiomeric peptide or peptide analogue according to formula (I).

61. (New) The ApoA-I agonist compound of Claim 60 in which one or two helical turns of the D-enantiomeric peptide or peptide analogue is optionally deleted.

62. (New) The ApoA-I agonist compound of Claim 1 which is an 18-residue D-enantiomeric peptide or peptide analogue according to formula (I).

63. (New) The ApoA-I agonist compound of Claim 62 in which
the "-" between residues designates -C(O)NH-;
Z_1 is H_2N-; and
Z_2 is -C(O)OH or a salt thereof.

64. (New) The ApoA-I agonist compound of Claim 63, in which;
X_1 is D-Ala (a), Gly (G), D-Asn (n) or D-Pro (p);
X_2 is D-Ala (a), D-Val (v), or D-Leu (l);
X_3 is D-Leu (l);
X_4 is D-Asp (d) or D- Glu (e);
X_5 is D-Leu (l) or D-Phe (f);
X_6 is D-Leu (l) or D-Phe (f);
X_7 is D-Arg (r), D-Lys (k) or D-Orn;
X_8 is D-Asp (d) or D-Glu (e);
X_9 is D-Leu (l) or D-Trp (w);
X_{10} is D-Leu (l) or D-Trp (w);
X_{11} is D-Glu (e) or D-Asn (n);
X_{12} is D-Glu (e);
X_{13} is D-Leu (l), D-Trp (w) or D-Phe (f);
X_{14} is D-Arg (r), D-Lys (k) or D-Orn;
X_{15} is D-Gln (q) or D-Asn (n);
X_{16} is D-Arg (r), D-Lys (k) or D-Orn;
X_{17} is D-Leu (l); and
X_{18} is D-Arg (r), D-Lys (k) or D-Orn.

65. (New) The multimeric ApoA-I agonist compound of Claim 16, 17 or 18 in which the bifunctional linker is cleavable.

66. (New) The multimeric ApoA-I agonist compound of Claim 16, 17 or 18 in which n is 0.

67. (New) The multimeric ApoA-I agonist compound of Claim 66 in which m is 0.

68. (New) The multimeric ApoA-I agonist compound of Claim 16, 17 or 18 in which each HH is independently an altered D-enantiomeric peptide or peptide analogue.

69. (New) The multimeric ApoA-I agonist compound of Claim 16, 17 or 18 in which each HH is independently a deleted D-enantiomeric peptide or peptide analogue.

70. (New) The ApoA-I agonist-lipid complex of Claim 25 in which the lipid is sphingomyelin.

71. (New) The pharmaceutical composition of Claim 33 in which the ApoA-I agonist is in the form of an ApoA-I agonist-lipid complex, said complex comprising the ApoA-I agonist compound and a lipid.

72. (New) The pharmaceutical composition of Claim 71 in which the lipid is sphingomyelin.

73. (New) The pharmaceutical composition of Claim 71 which is a lyophilized powder.

74. (New) The method of Claim 40 or 50 in which said subject is a human.

75. (New) The method of Claim 40 or 50 in which about 0.5 mg/kg to about 100 mg/kg ApoA-I agonist is administered to said subject.